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Revisiting *Terminalia arjuna* – An Ancient Cardiovascular Drug

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ABSTRACT

Terminalia arjuna, commonly known as *arjuna*, belongs to the family of Combretaceae. Its bark decoction is being used in the Indian subcontinent for anginal pain, hypertension, congestive heart failure, and dyslipidemia, based on the observations of ancient physicians for centuries. The utility of *arjuna* in various cardiovascular diseases needs to be studied further. Therefore, the present review is an effort to give a detailed survey of the literature summarizing the experimental and clinical studies pertinent to *arjuna* in cardiovascular disorders, which were particularly performed during the last decade. Systematic reviews, meta-analyses, and clinical studies of *arjuna* were retrieved through the use of PubMed, Google Scholar, and Cochrane databases. Most of the studies, both experimental and clinical, have suggested that the crude drug possesses anti-ischemic, antioxidant, hypolipidemic, and antiatherogenic activities. Its useful phytoconstituents are: Triterpenoids, β-sitosterol, flavonoids, and glycosides. Triterpenoids and flavonoids are considered to be responsible for its beneficial antioxidant cardiovascular properties. The drug has shown promising effect on ischemic cardiomyopathy. So far, no serious side effects have been reported with *arjuna* therapy. However, its long-term safety still remains to be elucidated. Though it has been found quite useful in angina pectoris, mild hypertension, and dyslipidemia, its exact role in primary/secondary coronary prevention is yet to be explored.

Key words: Antioxidant, Cardiovascular disorders, Coronary prevention, Flavonoids, *Terminalia arjuna*, Triterpenoids

INTRODUCTION

Arjuna is a potential cardioprotective agent belonging to the Combretaceae family. It is an ayurvedic remedy that has been mentioned since vedic period in many ancient Indian medicinal texts including Charaka Samhita, Sushruta Samhita, and Astang Hridayam. It was Vagabhatta who, for the first time, advocated the use of stem bark powder in heart ailments.[1]

ETHNOMEDICAL USES

The bark has been described as an astringent, demulcent, expectorant, cardiotonic, styptic, antidysenteric, urinary astringent, and has shown to be useful in fracture, ulcers, leukorrhea, diabetes, anemia, cardiopathy, and cirrhosis.[2] Chakradatta, the great ancient physician, recommended it to be given as a decoction of bark with milk or as a ghrita (a preparation with ghee or butter).[3] Decoction of the bark has been used as ulcer wash, while bark ashes have been prescribed for snakebite and scorpion sting.[4] Traditional healers from Kancheepuram district, Tamil Nadu boil the bark powder with water, and inhale it to cure headache and to kill worms in teeth. They also use fruit paste topically on wounds.[5] Fresh leaf juice is used for the treatment of earache and bark powder for treating heart ailments by Malabar tribe, Kerala.[6] Tribals living in Sundargarh District, Orissa use dried bark powder along with

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rice washed water to treat blood in urine, and tribes living in Malkangiri district chew the fresh bark and swallow the juice as an antacid.[7,8]

HABITAT

Arjuna tree is about 60-80 ft in height, and is seen along rivers, streams, and dry water bodies throughout the Indo-sub-Himalayan tracts of Uttar Pradesh, southern Bihar, Chota Nagpur, Burma, Madhya Pradesh, Delhi, and Deccan region [Figure 1]. It is also found in the forests of Sri Lanka and Mauritius.[3,9] It grows almost in all types of soils, but prefers humid, fertile loam and red lateritic soils. It can tolerate half submergence for a few weeks. *Arjuna* is propagated by seeds; Germination takes 50-70 days with 50-60% germination.[10]

PHARMACOGNOSTIC FEATURES

The outer surface of the bark is smooth, while the inner surface has longitudinal striation and is pinkish in color.[2] The bark gets flaked off itself in the month of April–May [Figure 2].[11]

On microscopic examination of the mature bark, a cork consisting of 9-10 layers of tangentially elongated cells, 2-4 cells thick phellogen, and phelloderm consisting of tangentially elongated cells are seen. The phloem is broad, consisting of ceratenchyma, phloem parenchyma, phloem fibers, and crystal fibers with rosette crystals of calcium oxalate. Periderm and secondary phloem are present in the old bark.[9,11,12]

Leaves are sub-opposite, coriaceous, oblong/elliptic, dull green from the upper side and pale brown on the lower side, often unequal sided with 10-15 pairs of nerves [Figure 3]. Flowers are white in color and bisexual, arranged in spikes with linear bracteoles [Figure 4]. Fruits are ovoid/oblong with 5-7 hard angles or wings. The lines on wings are oblique and curving upward [Figure 5].[2]

Major chemical constituents of *arjuna* have been shown in Table 1.[9,13-17]

Various extracts of the stem bark of *arjuna* have shown to possess many pharmacological properties including inotropic, anti-ischemic, antioxidant, blood pressure lowering, antiplatelet, hypolipidemic, antiatherogenic, and antihypertrophic.[18] Thus, in the present article, we have made an attempt to review and give up-to-date information pertinent to the usage of *arjuna* as a potential cardioprotective agent.

EXPERIMENTAL STUDIES

Effects on cardiac hemodynamics, coronary flow, and blood pressure

Bark stem of *arjuna* possesses diuretic, inotropic, and chronotropic properties.[9] In the Langendorff's rabbit heart preparation, the aqueous extract has demonstrated to cause an increase in the coronary flow.[19] Substantiating the earlier findings recently, an experimental study showed that the aqueous extract of *arjuna* increased the force of contraction of cardiac muscle in frog's heart *in situ*, hypodynamic frog's heart *in situ*, and isolated perfused rabbit heart. It increased the coronary flow in isolated perfused rabbit heart and produced bradycardia.[20] The inotropic effect is considered to be mediated through the high concentration of Ca^{++} present in the plant.[21]

Aqueous and alcoholic bark extract, when given intravenously, intracerebrally, and intravertebrally in dog, resulted in a

Figure 1. *Terminalia arjuna* tree

Figure 2. Bark stem of *Terminalia arjuna*

Figure 3. Leaves of *Terminalia arjuna*

dose-dependent decrease in blood pressure.[9] Singh *et al*. reported that an aqueous solution of 70% alcoholic bark extract produced dose-dependent decrease in heart rate and blood pressure in dogs, though the mechanism was not determined.[22]

Takahashi *et al*. demonstrated that the hypotensive effect of *arjuna* was observed with a fraction containing tannin-related compounds separated from the aqueous extract, which was not affected by pretreatment of rats with propranolol, but was attenuated by pretreatment with atropine. This suggested that the hypotensive effect may be mediated by cholinergic mechanisms.[23] Later on, it was documented that the 70% alcoholic extract produced dose-dependent hypotension of peripheral origin which might be due to adrenergic β2-receptor agonistic and/or direct action on the heart muscle. It was also suggested that muscarinic or histaminergic mechanisms are not likely to be involved in the hypotension produced.[24]

In a recent study, it has been established that the method of administration and/or selective omission of the hydrophobic components from the bark powder could be crucial to the efficacy and safety of *arjuna* bark in cardiac therapy.[25]

Antioxidant and cardioprotective effect

Dried, pulverized bark has been shown to augment endogenous antioxidant compounds of rat heart and prevent oxidative stress associated with ischemic–reperfusion injury of the heart.[26]

It was suggested that the alcoholic extract of *arjuna* in rabbit induces myocardial heat shock protein 72 and augments myocardial endogenous antioxidants which offer cardioprotection against oxidative stress associated with myocardial ischemic–reperfusion injury.[27] The cardioprotective effect of the active phytoconstituents of *arjuna* bark against carbon tetrachloride and sodium fluoride induced oxidative stress, probably via its antioxidant properties, has also been documented. In the above models, ferric

Figure 4. Flower of *Terminalia arjuna*

Figure 5. Fruits of *Terminalia arjuna* (ripe, fresh)

Table 1. Major chemical constituents of arjuna

Part of plant	Major chemical constituents	Major chemical constituents
Stem bark	Triterpenoids	Arjunin, arjunic acid, arjunolic acid, arjungenin, terminic acid, ajunglucosides IV and V, arjunasides A-E, 2-alpha, 3-beta-dihydroxyurs-12,18-dien-28-oic acid 28-O-beta-d-glucopyranosyl ester
	Glycosides	Arjunetin, arjunoside I, arjunoside II, arjunaphthanoloside, terminoside A
	Flavonoids	Arjunolone, arjunone, baicalein, luteolin, gallic acid, ethyl gallate, quercetin, kempferol, pelargonidin, oligomeric proanthocyanidins
	Tannins	Pyrocatechols, punicallin, punicalagin, terchebulin, terflavin C, castalagin, casuariin, casuarinin
	β-sitosterol	
	Minerals/trace elements	Calcium, aluminum, magnesium, silica, zinc, copper
Roots	Triterpenoids	Arjunic acid, arjunolic acid, oleanolic acid, terminic acid
	Glycosides	Arjunoside I, arjunoside II, arjunoside III, arjunoside IV, 2α,19α-dihydroxy-3-oxo-olean-12-en 28-oic acid 28-O-β-d-glucopyranoside
	β-sitosterol	
Leaves	Flavonoids	
	Alkaloids	
	Tannins	
	Steroids	
	Phenolic compounds	
	Oxalic acid	
	Inorganic acid	
Fruits	Glycosides	
	Flavonoids	Luteolin
Seeds	Cardenolide	14,16-dianhydrogitoxigenin-3-beta-d-xylopyranosyl (1-->2)-O-beta-d-galactopyranoside

reducing/antioxidant power assay revealed that ethanol extract enhanced the cardiac intracellular antioxidant activity.[28,29] In a recent study, the methanol extract yielded the highest phenolic and flavonoid content and was found to possess the highest total antioxidant capacity. Thus, it can be inferred that there exists a linear correlation between the antioxidant capacity and the total phenolic content of the extracts.[30] In another study, both alcoholic and aqueous extracts of the bark attenuated H_2O_2-mediated reactive oxygen species generation in human monocytic cells by promoting catalase and glutathione peroxidase (GPO) activities and by sustaining cellular reducing power. Moreover, the extracts inhibited lipid peroxidation (LPO) and 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, but had no effect on lipoprotein lipase.[31]

In isoprenaline-induced myocardial ischemia (MI), *arjuna* has been found to possess prostaglandin E2-like activity with coronary vasodilatation and hypotension.[1] The bark extract has shown to significantly prevent isoprenaline-induced increase in oxidative stress and decline in endogenous antioxidant level.

Arjunolic acid has been found to prevent the decrease in the levels of superoxide dismutase, catalase, GPO, ceruloplasmin, α-tocopherol, reduced glutathione, ascorbic acid, lipid peroxide, and myeloperoxidase.[32]

Further, the bark extract has also shown protective effects against doxorubicin-induced DNA damage and cardiotoxicity.[33,34] Kumar *et al*. demonstrated that *arjuna* protects the heart against myocardial changes induced by chronic β-adrenoceptor stimulation.[35] Substantiating this, in a recent experiment, the bark extract significantly attenuated cardiac dysfunction and myocardial injury in rats with congestive heart failure (CHF). Cardioprotective action of *arjuna* was comparable to fluvastatin. *Arjuna* bark extract has a significant prophylactic and therapeutic beneficial effect in protecting heart against catecholamine-induced CHF, possibly through maintaining endogenous antioxidant enzyme activities and inhibiting LPO and cytokine levels.[36]

Recently, Mythili *et al*. confirmed the earlier findings that triterpenoids derived from *arjuna* extract containing arjunolic acid show cardioprotective activity by boosting endogenous antioxidant defense system.[37]

Hypolipidemic and antiatherogenic activity

Earlier animal experiments have demonstrated that *arjuna* bark powder/extract reduces the total cholesterol (TC) and triglyceride (TG) levels.[38-41] On comparing the hypolipidemic property of the bark in different solvent fractions (petroleum ether, solvent ether, ethanol, and water) in hyperlipidemic rats, it was observed that only the ethanolic fraction exerted significant lipid-lowering effect. Solvent ether and ethanolic fractions caused a decrease in the plasma levels of lipids in triton as well as in high fat diet (HFD) fed models of hyperlipidemia in hamsters. In an *in vitro* experiment with *arjun*a fractions at concentrations of 50-500 μg/ml, they were found to inhibit the oxidative degradation of lipids induced by metal ions in human low density lipoprotein (LDL) and rat liver microsomes. When these fractions were tested against the generation of oxygen free radicals, they counteracted the formation of superoxide anions and hydroxyl radicals in nonenzymic test systems. The efficacy of *arjuna* fractions was found to be in the order: Ethanol fraction > solvent ether fraction > petroleum ether fraction.[42]

The ethanolic fraction possesses potent antioxidant and hypolipidemic properties compared to other fractions, and this has been substantiated by other studies also.[43,44] Subsequent work done by Sharma *et al*. also substantiated the hypolipidemic and antioxidant effect of *arjuna*. In addition to this, they also found that recipes (Arjuna Omelette and Arjuna En Upma) incorporating *arjuna* bark showed good acceptability, meriting their inclusion in the daily diet of the people needing long-term intervention for elevated lipids and oxidative stress levels.[45]

The hypolipidemic action is thought to be mediated through increased hepatic clearance of cholesterol, down-regulation of lipogenic enzymes, and inhibition of HMG-CoA reductase.[46] Further, Parmar *et al*. showed that there is a possibility of involvement of thyroid hormones (suppression of thyroid function) in the amelioration of cardiac and hepatic LPO by the bark extract in albino rats.[47]

CLINICAL USES

Angina/myocardial infarction

The anti-ischemic effect of bark powder was evaluated in 30 patients of stable angina/post-infarct angina (500 mg tds). The authors observed that the mean anginal frequency decreased significantly, along with a significant decrease in systolic blood pressure (SBP), improvement in ECG changes, and reduction in plasma cortisol and serum cholesterol levels.[48]

Later, in a study, 500 mg of bark powder was administered twice daily to 25 coronary artery disease (CAD) patients for 3 months. A reduction in the grade of positivity of treadmill test (TMT) response was observed in six patients, in addition to improvement in exercise tolerance and a reduction in the frequency of anginal attacks and use of sublingual nitrates.[49]

Subsequently, in an open-label trial, it was demonstrated that there was a 50% reduction in angina episodes along with a significant delay in the time to the onset of angina on TMT and appearance of ST–T changes in ECG after *arjuna* therapy was administered in stable angina patients. Significant lowering of SBP and body mass index, with a marginal improvement in left ventricular ejection fraction (LVEF) and a slight increase in high density lipoprotein (HDL) levels were also observed. In unstable angina patients, there was an insignificant reduction in anginal frequency. These results suggest that monotherapy with *arjuna* is fairly effective in patients with stable angina, but has a limited role in unstable angina.[50]

In yet another study, 500 mg of bark powder was administered 8 hourly to 10 patients of post-myocardial infarction angina and 2 patients of ischemic cardiomyopathy for a period of 3 months. These patients were compared with matched patients of post-myocardial infarction angina receiving only conventional treatment. Significant reduction in anginal frequency, improvement in LVEF (from 42.25 ± 9.96% to 52.57 ± 12.32%), and reduction in left ventricular mass (LVM; from 159.18 ± 51.11 g/m^2 to 140.62 ± 55.65 g/m^2) was noted.[51]

The efficacy of Hartone (an herbal product containing *arjuna*) was studied in 10 stable angina patients. The results were compared with those of 10 patients of stable angina on 20 mg of isosorbide mononitrate (ISMN) administered twice daily. It was observed that Hartone gave symptomatic relief in 80% of patients as compared to 70% in ISMN alone group. In addition, *arjuna* was better tolerated than ISMN.[52]

In a randomized, double-blind, cross-over study, 58 male patients with chronic stable angina (class II–III) with evidence of provocable ische mia on TMT received 500 mg of 90% alcohol extract 8 hourly, ISMN (40 mg/day), or a matching placebo for 1 week each after a washout period of at least 3 days. It was found that *arjuna* therapy was associated with a significant decrease in the frequency of angina and the need for isosorbide dinitrate. Improvements in clinical and TMT parameters were observed with both *arjuna* and ISMN as compared to placebo. No significant differences were observed in the above parameters when *arjuna* and ISMN therapies were compared.[53]

CHF/hypertension

In one of the earliest studies, 10 patients with CHF received 4 g of *arjuna* bark powder twice daily for 1 month. The researchers observed improvement in the functional class, breathlessness, and overall well-being with significant diuresis, and a fall in both systolic and diastolic blood pressure.[54]

Subsequently, the effect of bark extract (500 mg 8 hourly) was studied in a double-blind placebo-controlled two-phase trial comprising 12 patients with refractory CHF. In the first phase, *arjuna* was administered for a period of 2 weeks. A decrease in echo-left ventricular end-diastolic and end-systolic volume indices, an increase in left ventricular stroke volume index, and an increase in LVEF were recorded suggesting improvement. On long-term evaluation (20-28 months), in addition to continued improvement in symptoms and signs, they also reported an improvement in quality of life.[55]

A study done with abana (herbal formulation containing *arjuna*) in hypertensive individuals revealed an improvement in cardiac function as indicated by an increase in ejection fraction and a significant reduction of the SBP, echocardiographic left ventricular internal diameter, posterior wall thickness, and interventricular septal thickness.[56]

Recently, *arjuna* has also been shown useful in improving cardiovascular endurance and in lowering SBP in normal healthy subjects.[57]

Rheumatic heart disease

Efficacy of *arjuna* in decompensated rheumatic heart disease was studied in a double-blind study in which 30 patients of rheumatic valvular heart disease with CHF were administered 200 mg *arjuna* thrice daily. The results revealed a significant improvement in LVEF, exercise duration, and significant reduction in heart size.[58]

Ischemic mitral regurgitation

In a randomized, double-blind, placebo-controlled study done in patients with ischemic mitral regurgitation (IMR) following acute myocardial infarction, *arjuna* was found to significantly decrease IMR and anginal frequency. In addition, there was also significant improvement in diastolic dysfunction (E/A ratio; from 0.93 ± 0.31 to 1.38 ± 0.40 at 12 weeks).[59]

Cardiomyopathy

In addition to its anti-ischemic property, *arjuna* was found to reduce LVM and improve LVEF.[59] A recent observational study revealed that when patients of dilated cardiomyopathy with reduced LVEF received *arjuna* in addition to their standard therapy, there was a significant improvement in left ventricular parameters as well as functional capacity.[60]

Platelet aggregation

The bark extract has been found to decrease platelet activation and possess antithrombotic properties *in vitro* in 20 patients of angiographically proven CAD and 20 age- and sex-matched controls. The possible mechanism could be by desensitizing platelets by competing with platelet receptor or by interfering with signal transduction.[61]

In another recent randomized, double-blind, parallel-group, placebo-controlled study in patients with type 2 diabetes mellitus, 500 mg of *arjuna* administered thrice daily resulted in a significant increase in mean cardiac output from 4.34 ± 0.38 to 4.86 ± 0.20 (l/min). In addition to this, there was a reduction in mean systemic vascular resistance from 1729 ± 93.52 to 1484 ± 115.5 (dyne sec/cm^5). *Arjuna* also caused significant inhibition of platelet aggregation.[62]

Oxidative stress/dyslipidemia

In a study on 21 patients with coronary heart disease administered 1 g of bark powder twice daily with milk for 4 months, the patients showed improvement in lipid profile. In addition to this, patients got symptomatic relief after 1 month of treatment.[63]

Antioxidant effect of bark powder (500 mg) has been demonstrated to be comparable to vitamin E (400 IU) in a randomized, controlled, open trial done in 105 patients with coronary heart disease. The authors also observed a significant decrease in TC, LDL, and lipid peroxide levels. The hypocholesterolemic effect was attributed to the soluble fibers and sitostanol content, while the antioxidant effect was attributed to the flavonoids.[64] Further, it was observed in a study that when the bark powder was given along with statin for 3 months, it resulted in 15% reduction in TC, 11% reduction in TG, and 16% reduction in LDL, while there was minimal decline in lipoprotein (a) and nitrite levels.[65]

In a prospective cohort study, dyslipidemic patients received *arjuna* powder (5 g, BD) for 3 weeks followed by Arogyavardhini Vati (500 mg, BD) for 4 weeks. A significant reduction in TC, LDL, TG, serum C-reactive protein, blood glucose, and an increase in HDL level were found, which supported the role of *arjuna* in dyslipidemic patients.[66]

Lipoprotein(a)

A significant reduction in lipoprotein(a) levels amounting to 24.71% following the administration of *arjuna* in a patient of β-thalassemia associated with hyperlipoproteinemia and metabolic syndrome has been reported.[67]

Endothelial dysfunction

In a double-blind, placebo-controlled, cross-over study involving 18 healthy male smokers and an equal number of age-matched non-smoker controls, it was observed that the hydroalcoholic extract of bark when given for 2 weeks led to significant regression of the endothelial abnormality amongst smokers.[68]

Thrombotic condition

In a recent study done to investigate the *in vitro* thrombolytic and membrane-stabilizing action of four Bangladeshi medicinal plants including *arjuna*, the methanol extract was found to possess significant thrombolytic activity (30.57%). It also significantly inhibited the hemolysis of RBCs in both hypotonic solution and heat-induced conditions. This showed that it has moderate thrombolytic activity; however, more research is needed to isolate the secondary metabolites responsible for the activity.[69]

Not much data is available to comment on the effect of *arjuna* on cytochrome P450 (CYP450) enzyme. Results from a recent *in vitro* study indicate that *arjuna* extracts contain constituents that can potently inhibit the activity of CYP1A.[70]

TOXICITY AND SIDE EFFECTS

Mild side effects like nausea, gastritis, headache, bodyache, constipation, and insomnia have been reported. No hematological, renal, or metabolic toxicity has been reported even after more than 24 months of its administration.[48,50,53,55] However, Parmar *et al*. noticed that administration of *arjuna* resulted in reduction of thyroid hormone concentration in euthyroid animals, whereas the hepatic LPO was increased. Thus, high amounts of the plant extract should not be consumed, as it may induce hepatotoxicity as well as hypothyroidism.[47] The results from a recent acute and oral toxicological study done in animals showed that administration of ethanolic extract at a limit dose of 2000 mg/kg orally did not produce any kind of toxicity and death in animals.[46]

CONCLUSION

The eternal interest in medicinal plants has led to the discovery of new chemical constituents and pharmacological actions of *arjuna*. Its efficacy as an anti-ischemic agent, a potent antioxidant, and an antiatherogenic agent has been amply demonstrated in various experimental and clinical studies. However, major lacunae of these studies include the lack of phytochemical standardization of the extract, bioavailability studies, and well-designed studies to evaluate its long-term toxicity effects. Its exact role in primary/secondary coronary prevention needs to be investigated. In addition to this, studies to look for the effect of *arjuna* on CYP450 enzymes and its interactions with other drugs like statin, aspirin, angiotensin-converting enzyme (ACE) inhibitors, and β-blocker need to be designed. Increasing the awareness regarding its medicinal usage can give a direction to the physicians to respond to the challenges in treating cardiovascular diseases.

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